0013-7227/05/$15.00/0
Printed in U.S.A.

Endocrinology 146(9):3718–3723

doi: 10.1210/en.2005-0411

Minireview: Role of the Growth Hormone/Insulin-Like Growth Factor System in Mammalian Aging

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The important role of IGF and insulin-related signaling pathways in the control of longevity of worms and insects is very well documented. In the mouse, several spontaneous or experimentally induced mutations that interfere with GH biosynthesis, GH actions, or sensitivity to IGF-I lead to extended longevity. Increases in the average life span in these mutants range from approximately 20–70% depending on the nature of the endocrine defect, gender, diet, and/or genetic background. Extended longevity of hypopituitary and GH-resistant mice appears to be due to multiple mechanisms including reduced insulin levels, enhanced insulin sensitivity, alterations in carbohydrate and lipid metabolism, reduced generation of reactive oxygen species, enhanced resistance to stress, reduced oxidative damage, and delayed onset of age-related disease. There is considerable evidence to suggest that the genetic and endocrine mechanisms that influence aging and longevity in mice may play a similar role in other mammalian species, including the human. (*Endocrinology* 146: 3718–3723, 2005)

THE SOMATOTROPIC AXIS, consisting of pituitary-derived GH and IGF-I, the main mediator of GH actions, is the key determinant of somatic growth and adult body size. Moreover, the GH/IGF-I system is involved in the regulation of puberty and gonadal function and influences body composition as well as structural and functional maintenance of adult tissues. Loss of skeletal muscle mass, increased adiposity, and other unwelcome accompaniments of aging have been linked to age-related decline in pituitary GH secretion (1) and some of these changes can be ameliorated by GH treatment of elderly individuals (1, 2). On this basis, administration of GH is often advocated as an "anti-aging" therapy (3). In sharp contrast to these findings, GH deficiency, GH resistance, and reduced IGF-I signaling in mice are associated with symptoms of delayed aging and markedly extended longevity (4–7). Although most normal mice die at approximately 2 yr of age, hypopituitary and GH-resistant mutants often survive beyond the age of 3 yr and occasionally past the age of 4 yr, *i.e.* outside the range encountered in various laboratory strains of this species. In this brief review, we will list the key characteristics of long-lived GH-deficient, GH-resistant, and IGF-I-resistant mice, discuss mechanisms that are believed to link reduced somatotropic signaling with prolonged longevity, and speculate on the possible relevance of findings obtained in genetically altered mice to the physiological control of aging in normal mice and in other mammalian species including the human.

Long-Lived Mutant Mice

Primary defects in somatotropic signaling and some of the secondary endocrine changes in different types of long-lived mutant mice are listed in Table 1. In three of these mutants [Ames dwarf, Snell dwarf, and GH receptor knockout (GHRKO)], robust increases in longevity were reproducibly observed in both genders (4–6, 9, 13–15). In addition, increased longevity of GHRKO mice was observed in different laboratories (5, 13, 14) and in stocks with different genetic backgrounds (13). In "little" ($GHRHR^{lit}$) mice, significant extension of longevity was detected only when the animals were fed a low-fat diet to prevent obesity (6). In $IGFIR^{+/-}$ mice, extension of average life span was significant only in females (7). However, it should also be mentioned that $IGFIR^{+/-}$ mice are unique among these long-lived mutants by having near-normal growth and adult body size and no detectable alterations in reproductive development and function (7). Preliminary findings from ongoing studies in mice expressing a hypomorphic IGF-I mutation support the conclusion that reduction of IGF-I signaling in mice leads to increased longevity (C. Sell, personal communication). Surprisingly, life span is not altered in transgenic mice expressing an antagonistic analog of GH (13). We suspect that this may be due to a very modest reduction in circulating IGF-I levels in these animals (13). Moreover, in contrast to GH-deficient and GH-resistant mutants, GH antagonist transgenic mice exhibit no reduction in insulin and only very minor, age-dependent suppression of glucose levels (13), with some of these characteristics likely being related to conspicuous obesity of these animals.

With the exception of $IGFIR^{+/-}$ animals, mice with mutations affecting somatotropic signaling exhibit a series of phenotypic characteristics consistent with GH deficiency or resistance including reduced postnatal (and particularly, postweaning) growth, diminutive adult body size, delayed puberty, and reduced fertility. In addition, Ames and Snell dwarf as well as GHRKO mice have reduced plasma insulin and glucose levels (16–19). Snell and Ames dwarf mice have primary endocrine defects unrelated to the somatotropic axis. Both of these mutants lack thyroid stimulating hormone and, therefore, are hypothyroid and are also prolactin (PRL)-

First Published Online May 26, 2005

Abbreviations: GHRKO, GH receptor knockout; PRL, prolactin; ROS, reactive oxygen species.

***Endocrinology* is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**

TABLE 1. Mutations that alter somatotropic signaling and increase longevity in the mouse

Name and frequently used symbols	Origin and first description	Primary effect	Kay phenotypic characteristics	Increase of average longevity
Ames dwarf; df; Prop1^{df}	Spontaneous mutation; Schaible and Gowen, 1961 (8)	Failure of differentiation of somatotrophs, lactotrophs, and thyrotrophs; primary deficiency of GH, PRL, and TSH	Reduced growth and adult body weight; undetectable plasma GH, PRL, TSH, and IGF-I; reduced plasma levels of thyroid hormones, insulin, and glucose; female sterility due to luteal failure; reduced oxidative damage	35–70% depending on gender and diet (4, 9)
Snell dwarf; dw, Pit1^{dw}	Spontaneous mutation; Snell, 1929 (10)			~42% (6)
Little lit; GHRHR^{lit}	Spontaneous mutation; Eicher and Beamer, 1976 (11)	GHRH resistance; suppression of GH release	Reduced growth and body weight of young adults; progressive increase in adiposity	24% (only if fed low-fat diet) (6)
GHR/GHBP knockout; Laron Dwarf; GHR/GHBP-KO; GHR-KO	Targeted gene disruption; Zhou *et al.*, 1997 (12)	Absence of GH receptor and binding protein; GH resistance	Reduced growth and adult body size; reduced plasma IGF-I, insulin, and glucose; increased plasma GH; increased adiposity; quantitative reduction of fertility parameters	40–55% on heterogeneous genetic background; 26% in males on C57BL/6 background (5, 13)
IGFIR heterozygous Knockout; IGFIR+/−	Targeted gene disruption; Holzenberger *et al.*, 2003 (7)	Reduced number of IGF-I receptors; partial IGF-I resistance	Normal fertility; slight reduction in body weight; increased resistance to oxidative stress	33% in females and a suggestive increase in males (7)

deficient. Reduction of body temperature in dwarf mice (20) is presumably related to hypothyroidism, although lack of GH and reduced levels of insulin are likely to contribute to this characteristic. PRL deficiency leads to female sterility, because in the mouse, PRL is absolutely required for luteal function, implantation, and maintenance of pregnancy (21).

In hypopituitary Ames and Snell dwarf mice as well as in GH-resistant GHRKO mice, a significant increase in life span is associated with various symptoms of delayed aging (Table 2). These findings suggest that the biological process of aging is altered in these animals and their increased life expectancy is not due to removing causes of early mortality.

Suspected Mechanisms of Prolonged Longevity

Association of reduced somatotropic signaling with extended longevity in laboratory stocks of house mice (*Mus musculus*) is robust, reproducible, and consistent across several mutants, genetic backgrounds, and diets (4–7, 13–15, 22). However, at this point, we can only speculate which of the seemingly endless list of direct and indirect consequences of GH deficiency or resistance are causally related to prolonged longevity. In Snell and Ames dwarf mice, the situation is further complicated by concomitant PRL and thyroid stimulating hormone deficiency, the likely importance of hypothyroidism, and possible interactions between the consequences of different hormonal deficits. Despite these limitations, studies conducted to date and comparisons with data obtained in genetically normal animals in which life span was extended by reducing the amount of food they are allowed to consume (the so called "caloric restriction") suggest several potential mechanisms that may link reduced GH/IGF-I signaling with delayed aging.

TABLE 2. Evidence for delayed aging of hypopituitary and GH-resistant mice

Symptoms	Mutants	Refs.
Increased maximal life span	Ames dwarf	4, 22
	Snell dwarf	6
	GHRKO	13, 14
Increased mortality rate doubling time	Snell dwarf	6, 23
	GHRKO	23
Delayed/reduced neoplasms and other age-related disease	Ames dwarf	24
	Snell dwarf	15
	GHRKO	[a]
Maintenance of cognitive function	Ames dwarf	25
	GHRKO	26
Delayed cartilage aging and arthrosis	Snell dwarf	27
Delayed collagen aging	Snell dwarf	6
Delayed immune aging	Snell dwarf	6

[a] Ikeno, Y., and A. Bartke, unpublished observation

Metabolic rate and oxidative damage

Reduced levels of GH, IGF-I, insulin, and thyroid hormone would be expected to lead to reduced oxidative metabolism and reduced generation of reactive oxygen species (ROS), two very plausible mechanisms of delayed aging. Reduced oxygen consumption (28), body core temperature (20, 29) and mitochondrial ROS production (30), combined with increased expression and/or activity of enzymes involved in antioxidant defenses (31–34) in hypopituitary and/or GH-resistant mice are consistent with the suspected importance of these mechanisms. In further support of the role of reduced ROS production and enhanced antioxidant defenses as potential mechanisms of delayed aging, oxidative damage of proteins, lipids, and mitochondrial DNA are reduced in Ames dwarf mice (30, 35).

Stress resistance

It was recently shown that skin fibroblasts isolated from either Snell dwarf, Ames dwarf, or GHRKO mice survive significantly longer than fibroblasts isolated from normal mice when exposed to various forms of cytotoxic stress *in vitro* (36, 37). Association of increased stress resistance with delayed aging and extended longevity was described previously in long-lived invertebrate mutants (38) and in mammals subjected to caloric restriction (39).

Insulin signaling

Hypoinsulinemia combined with enhanced sensitivity to insulin and reduced or "low normal" glucose levels represent another likely mechanism of extended longevity of GH-deficient and GH-resistant mice (Fig. 1). Reduced mass of pancreatic islets (17, 40), absence of "anti-insulinemic" actions of GH, enhanced secretion of adiponectin (41), and altered expression of genes related to insulin sensitivity including peroxisome proliferators activated receptor γ and its coactivator PGC1α (41–43, 78) are among likely mechanisms of reduced insulin release and enhanced insulin sensitivity in these animals. It is well documented that reduced function of homologous (IGF/insulin-like) signaling pathways leads to major extension of life span in worms and flies (reviewed in Refs. 44 and 45). In the human, centenarians were reported to be exceptionally insulin sensitive (46) and to have reduced incidence of diabetes (47). These characteristics of exceptionally long-lived people are remarkable, because human aging is normally associated with a progressive increase in insulin resistance and a significant age-related reduction in insulin sensitivity was evident in normal individuals from the same population (46). Moreover, insulin resistance and "metabolic syndrome" (a condition roughly opposite to the characteristics of insulin signaling in dwarf and GHRKO mice) is a major risk factor for age-associated diseases (48).

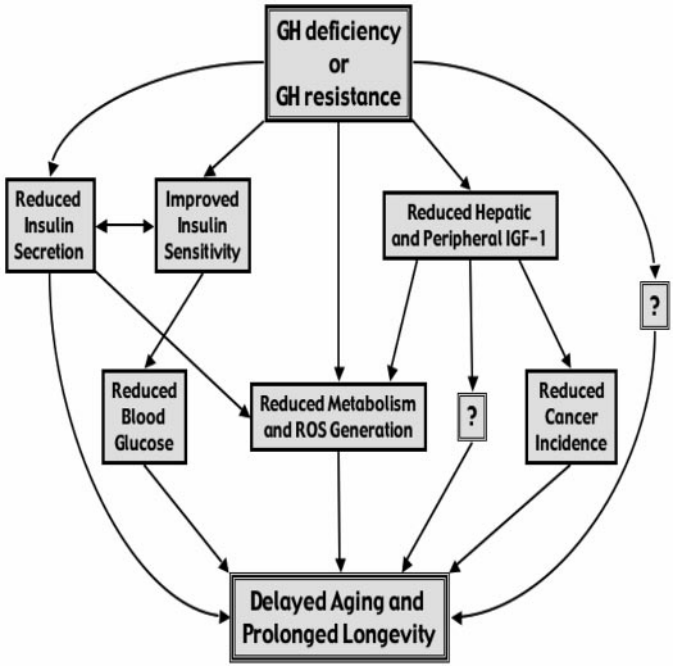

FIG. 1. Proposed mechanisms of prolonged longevity of hypopituitary, GH-deficient, and GH-resistant mice.

Recent findings raise an interesting possibility that in the absence of GH signaling, the actions of lactogenic hormones during early development may set the stage for enhanced insulin sensitivity in adult life. Fleenor *et al.* (49) reported that mice with combined GH deficiency and PRL resistance (created by crossing little $GHRHR^{lit}$ and PRL receptor knockout animals) develop insulin resistance and characteristics of metabolic syndrome. This contrasts sharply with the situation described previously in Ames dwarf mice in which combined GH and PRL deficiency is associated with enhanced rather than reduced sensitivity to insulin (18). It is tempting to ascribe this difference to the inability of PRL receptor knockout mice to respond to placental lactogens and maternal PRL (including PRL present in the milk) during prenatal and early postnatal development. However, in adult mice, lactogenic (PRL receptor-mediated) signaling presumably plays little role in regulating sensitivity to insulin since enhanced responses to insulin are present in both Ames dwarfs that are PRL deficient (18, 21) and GHRKO mice (17) that are mildly hyperprolactinemic (50).

Body size: data from normal mice and other species

Diminutive body size is a striking characteristic of most long-lived mouse mutants. Association of small stature with prolonged longevity applies also to genetically normal mice and is supported by meta-analysis of multiple studies (51) and by the recent demonstration that small body size is a significant predictor of longer lifespan in individual animals from a genetically heterogeneous population of normal mice (52). Negative correlation of body size and longevity is well documented in domestic dogs (53, 54) and in laboratory stocks of rats (51) and was reported also in other species including the human (55). Presumably, small stature is a phenotypic marker of some developmental and/or metabolic characteristics that predispose to increased life expectancy. However, reduced body size *per se* is unlikely to lead to delayed aging. Vergara *et al.* (15) recently reported that 7 wk of treatment of young Snell dwarf mice with GH or GH plus thyroxine failed to shorten their lifespan even though it significantly increased their adult size.

Gonadal function

Important interactions between the somatotropic and the hypothalamic-pituitary-gonadal axes and numerous examples of trade-offs between longevity and fecundity (56) suggest that delayed reproductive development and reduced fertility of long-lived mutant mice could be contributing to their extended survival. Existence of such a relationship would be consistent with a concept of antagonistic pleiotropy. Thus, high levels of GH and IGF-I would be favored by natural selection because of their positive impact on sexual maturation and reproductive competence, but would exert negative impacts (*e.g.* promoting tumorigenesis or accelerating the rate of aging) later in life when the force of natural selection is diminished. However, the potential impact of reduced reproductive competence on aging in hypopituitary and GH-resistant mice appears to be very minor. Compara-

ble life extension and similar maximal life spans were recorded among Snell dwarf mice from a stock in which dwarfs are sterile (6), Snell dwarfs rendered fertile by hormone therapy (15), Ames dwarf mice from a stock in which many females cycle and most males are fertile (4), and in GHRKO mice, in which both sexes can reproduce (12).

Alterations at the Level of Gene Expression

Microarray analysis of wide profiles of gene expression (43, 57, 58) and real-time PCR studies of genes related to insulin and IGF-I signaling in various organs (41, 42, 79) strengthen the evidence for reduced IGF-I/insulin signaling in long-lived mutant mice, and demonstrate alternations in gene expression that are consistent with enhanced insulin sensitivity and oxidative stress resistance in these animals. Results of these studies also suggest a possible role of enhanced gluconeogenesis and β-oxidation of fatty acids and reduced glycolysis and lipogenesis in the liver, as well as increased expression of Foxo family forkhead transcription factors, peroxisome proliferators-activated receptor γ, and PGC1α in extending longevity of GH-deficient or GH-resistant mice. Reduced lipogenesis in long-lived mutant mice is strongly supported by elegant studies of various steps of cholesterol biosynthesis in the liver of Snell dwarf mice (59). Interestingly, adiposity as measured by percent of body fat is increased rather than decreased in GHRKO and in young adult Ames dwarf mice (60, 61). We suspect that coexistence of adiposity and enhanced insulin sensitivity in long-lived mouse mutants is due to altered secretion of adiponectin, TNFα, and IL-6 by fat cells of these animals (41, 80).

Brain IGF-I and cognitive function

Demonstration of enhanced IGF-I expression in the hippocampus of Ames dwarf mice (62, 63) raised an intriguing possibility that preservation and/or compensatory increases in the local production and paracrine/autocrine actions of IGF-I may account for some unexpected phenotypic characteristics of long-lived GH-deficient mutants. Ames dwarf and GHRKO mice do not differ from normal animals in performance of tasks designed to measure learning and memory (25, 26). Moreover these animals maintain youthful levels of cognitive function into a very advanced age (25, 26, 64) despite deficiency of GH signaling and reduction of circulating IGF-I below the level of detectability. Both GH and IGF-I are well documented to exert important neurostimulatory and neuroprotective effects (65, 66). We suspect that the paradox of apparently normal cognitive function and its preservation during aging in animals with deficient somatotropic signaling may be due to normal or enhanced IGF-I biosynthesis and actions in brain regions providing neural substrate for learning and memory.

Somatotropic Axis and Longevity of Rats

Although results obtained in rats are in general agreement with the data concerning the effects of GH and IGF-I on aging, some important differences also exist. Heterozygous transgenic rats expressing antisense GH live longer than normal rats, but animals homozygous for the expression of the same transgene have a reduced rather than extended life span (67). Longevity is not affected in dwarf rats which are GH deficient and have plasma IGF-I levels reduced to approximately 50% of normal values (68). Intriguingly, adult onset GH deficiency produced in dwarf rats by GH replacement therapy between 4 and 14 wk of age increased longevity of males significantly above the values measured in either mutated dwarf rats or their normal siblings (68). In the Lou C/Jall rats which are long-lived, lean, and were described as a model of healthy aging, pulsatile GH secretion is maintained during aging, but IGF-I levels are reduced and exhibit a pronounced age-related decrease, implying partial GH resistance (69). Results of meta-analysis of data from over 400 groups of rats revealed significant negative correlation of maximal body size with maximal longevity in this species (51) resembling data obtained in mice.

Relevance to the Human

Can the findings in mice summarized above be extrapolated to the human? This question is not easy to answer. Because mutations affecting IGF-I/insulin or homologous signaling pathways exert major effects on longevity in organisms ranging from unicellular yeast, through worms and insects, to rodents, it seems entirely reasonable to expect that the involvement of these signaling pathways in the control of aging is universal and includes humans. In the human, some individuals with hypopituitarism due to Prop1 mutations (homologous to Ames dwarfism in mice), or with Laron dwarfism (GH resistance, equivalent to the phenotype of GHRKO mice) can survive into very advanced age (70, 71), but dwarfs with isolated GH deficiency were reported to have reduced life span (72). Pathologically elevated levels of GH are associated with reduced life expectancy in both acromegalic humans (73, 74) and transgenic mice (reviewed in Ref. 75). However, increased mortality rate of acromegalics is due mostly to greater incidence of cardiovascular disease, diabetes, and cancer and thus it could be debated whether the biological process of aging *per se* is altered in these individuals. As was mentioned earlier in this *Minireview*, there is also evidence that a negative correlation of body size and longevity, which is very robust in mice and dogs, may apply to the human (55). Association of greater height with shorter lifespan was very striking in some of the examined cohorts, for example in professional baseball players (55). Height can be assumed to represent a biomarker of the activity of the somatotropic axis, including circulating IGF-I levels and responsiveness of target tissues to IGF-I.

Studies of polymorphic variants of genes related to GH biosynthesis, IGF-I signaling and insulin action (47, 76, 77), provided evidence for altered frequency of several of these variants in exceptionally long-lived people. For example, Kojimra *et al.* (47) recently reported that one insulin receptor haplotype comprised of two SNPs in linkage disequilibrium was significantly more frequent in semisuper centenarians (individuals who were 105 yr old or older) than in healthy younger controls. A study by van Heemst *et al.* (76) examined frequency of variants of five genes related to GH and insulin signaling in relation to height and longevity in humans. Based on the expected effects of these genetic variants on

hormonal signaling, these authors concluded that a composite score reflecting low activity of this pathway was significantly associated with lower height and improved old age survival in women. Carriers of a SNP variant of the GH1 gene were shorter by 2 cm and had 0.80-fold reduced mortality compared with carriers of a wild-type allele (76). Increased insulin sensitivity in centenarians (46) and detrimental effects of insulin resistance (48) mentioned earlier in this review provide additional indications that at least some of the suspected mechanisms of delayed aging in mice with reduced somatotropic signaling may apply broadly, including humans.

Acknowledgments

Apologies are extended to all those whose findings or opinions pertinent to this topic were not referenced or discussed due to limitations of space or inadvertent omissions.

Received April 11, 2005. Accepted May 17, 2005.

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This work was supported by the National Institutes of Health (RO1 AG19899 and 1U19 AG023122-01A) and by the Ellison Medical Foundation.

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***Endocrinology* is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**